VIRTUAL 2020 ESMO congress

Gastrointestinal toxicity: From the top to the bottom

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DISCLOSURE INFORMATION

I have received honoraria for speaker engagemenets and advisory board participation by:

Merck, Sanofi, Merck Sharp & Dohme, Sun Pharma, Angelini, AstraZeneca, Bristol-Myers Squibb, Helsinn, Kyowa Hakko Kirin, Roche, GSK

Mucositis: how to assess it and how to predict the risk

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HOW TO ASSESS ORAL MUCOSITIS

The importance of relying on **patient reported outcome instruments**

PROMs	VAS: mouth pain, difficulty speaking, restriction of speech, difficulty and restriction eating/drinking, difficulty swallowing, changes in taste
OMQoL	4-point Likert scale: symptomatology of mucositis and swallowing; nutrition, social function
OMWQ-HN OMDQ	Likert-type response: mouth and throat pain and its impact on well-being and function
PRO-CTCAEs	Libraries of PROMs
FACT-G; EORTC QLQ HN35/43	Mucositis scales assessed within general construct of QoL

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RISK PREDICTION

- Defining the risk profile of the patient before starting treatment is essential to promptly recognize the toxicity and to early implement a supportive care protocol

- Evaluate patient, disease and treatment related risk factors

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RISK PREDICTION

Patient-related

Supportive Care in Cancer (2020) 28:5059–5073
https://doi.org/10.1007/s00520-020-05579-7

REVIEW ARTICLE

Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action

Factor	Mucositis type	Level of evidence
Demographic and lifestyle factors		
Female sex	OM*	++
	GI-M*	+
Age (extremities)	OM*	+
Smoking	OM*	++
Low BMI	OM*	+
Performance status	OM	+
	GI-M	+
Neutropenia < 500 mm^3	GI-M	+
High serum creatinine	OM	+
Low DPD activity	OM	+
	GI-M	+
Leukopenia/lymphopenia	OM*	+
Hemoglobinemia	OM	+
Low platelets	OM	+
Renal dysfunction	OM	+
HPV diagnosis	OM*	+
IBD/high number of daily bowel movements	GI-M	+
Recent antibiotic use	OM	+
	GI-M	+
Use of tongue immobilizer	OM	+
Lack of oral care protocol	OM*	+
Oral feeding (versus tube)	OM	+

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Gene	Mucositis type	Level of evidence
Drug-metabolizing/efflux pathways		
MTHFR	OM	+++
	GI-M*	+++
UGT1A1	GI-M	++
DPYD	OM	+++
	GI-M	+++
TYMS	OM*	++
	GI-M	++
DPYS	OM	+
IVS1	GI-M	+
CYP2B6	OM	+
ABCC1	OM	+
Cell growth/repair pathways		
NBN	OM	+
TGFB	GI-M	+
ERCC1	GI-M	+
RAD51	GI-M	+
VEGFR2	GI-M	+
ATM2/2	GI-M	+
RPM1	OM	+
MDM2	OM	+
CCND	OM	+
XRCC1	OM*	++
	GI-M	++

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Disease-related

Factor	Mucositis type	Level of evidence
Orally located tumor	OM	+
Stage	OM	+
Volume	OM	+
Germinal (versus non-germinal) tumor	OM	+
Hematological (versus CNS) malignancy	OM	+

HPV

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RISK PREDICTION

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REVIEW ARTICLE

Prediction of mucositis risk secondary to cancer therapy: a systematic review of current evidence and call to action

Treatment-related

Factor	Mucositis type	Level of evidence
Cumulative dose	OM	++
	GI-M	+
Irradiation volume/area	OM	+
	GI-M	+++
Duration of therapy	OM	+
Concurrent chemotherapy	OM	++
Conditioning therapy containing TBI, busulfan, melphalan, etoposide	OM	+
Conditioning therapy containing doxorubicin	GI-M	+
Myeloablative or fully ablative (versus non-myeloablative) conditioning	OM	++
	GI-M	+
Altered fractionated RT (versus once daily)	OM	+
3DCRT (versus IMRT)	GI-M	++
Infusion (versus bolus)	OM/GI-M	+
Evening radiotherapy	OM	+
Morning radiotherapy	GI-M	+

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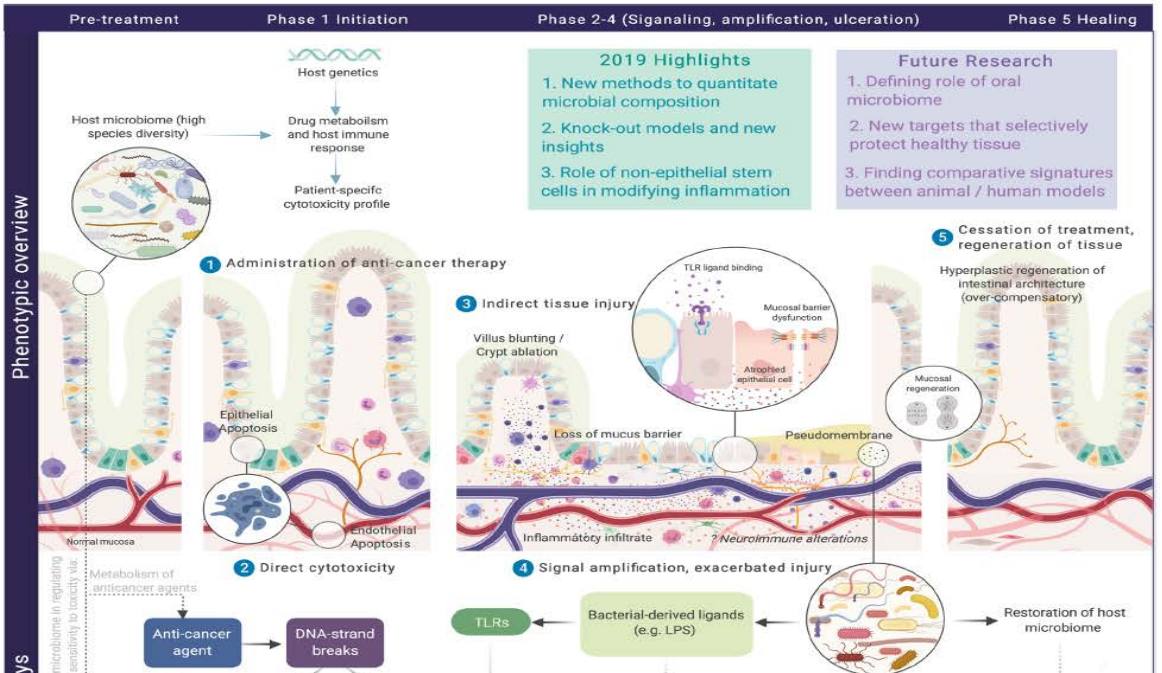
FOCUS ON PATHOGENETIC MODELS



FOCUS ON PATHOGENETIC MODELS: NEWS

✓ Microbiome and host interaction	→	Baseline for risk stratification and modification Dynamic changes during treatment
✓ Host innate immune response	→	TLR role – innate lymphoid cells
✓ Inflammatory-based mechanisms	→	Proinflammatory cytokines – upstream modulators of ROS
✓ Neuroimmune signalling	→	Enteric glia and specific neuronal cells

Mucositis: new MASCC guidelines

Original Article

MASCC/ISOO Clinical Practice Guidelines for the Management of Mucositis Secondary to Cancer Therapy

Sharon Elad, DMD, MSc[1]; Karis Kin Fong Cheng, RN, PhD[2]; Rajesh V. Lalla, DDS, PhD[3]; Noam Yarom, DMD[4]; Catherine Hong, BDS, MS[5]; Richard M. Logan, BDS, MDS, PhD[6]; Joanne Bowen, PhD[7]; Rachel Gibson, PhD[8]; Deborah P. Saunders, DDS[9]; Yehuda Zadik, DMD, MHA[10]; Anura Ariyawardana, BDS, MS[11]; Maria Elvira Correa, DDS, PhD[12]; Vinisha Ranna, DDS[13]; and Paolo Bossi, MD[14]; for the Mucositis Guidelines Leadership Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO)

Cancer, 2020

Basic Oral Care (BOC)

Intervention: Professional oral care

	LoE	Guideline category	Guideline
1	III	NGP / Expert opinion	• Dental evaluation and treatment as indicated prior to cancer therapy is desirable to reduce the patient's risk for local and systemic infections from odontogenic sources.

Basic Oral Care (BOC)

Intervention: Multi-agent combination oral care protocols

	LoE	Guideline category	Guideline
2	III	Suggestion	• The panel suggests that implementation of multi-agent combination oral care protocols is beneficial for the prevention of OM during **CT – H&N RT - HSCT**

Basic Oral Care (BOC)

Intervention: Patient Education

	LoE	Guideline category	Guideline
5	III	NGP / Expert opinion	• The panel is of the opinion that educating patients about the benefits of BOC strategies is still appropriate as this may improve patient's self-management and adherence to the recommended oral care protocol during cancer treatment.

Basic Oral Care (BOC)

Intervention: Bland Mouth Rinses

	LoE	Guideline category	Guideline
6	III	NGP / Expert opinion	• Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these rinses are inert bland rinses that increase oral clearance which may be helpful for maintaining oral hygiene and improving patient comfort.

Basic Oral Care (BOC)

Intervention: Chlorhexidine

	LoE	Guideline category	Guideline
7	III	Suggestion against	• The panel suggests that CHX not be used in the prevention of OM in patients undergoing **H&N RT**.

Anti-inflammatory

Intervention: Benzydamine

	LoE	Guideline category	Guideline
8	I	Recommendation	• Benzydamine mouthwash is recommended for the prevention of OM in patients with **H&N** cancer receiving a **moderate dose RT** (<50 Gy).
9	II	Suggestion	• Benzydamine mouthwash is suggested for the prevention of OM in patients with **H&N** cancer receiving **RT and CT**.

PBM (Laser/light) therapy

	LoE	Guideline category	Guideline
10	I	Recommendation	• The panel recommends the use of intra-oral PBM therapy using low level laser therapy for the prevention of OM in adult patients receiving **HSCT** conditioned with high-dose CT, with or without total body irradiation using one of the selected protocols in Table 1

Protocol	Wavelength (nm)	Power density (irradiance; mW/cm^2)	Time per spot (sec)	Energy density (fluence; J/cm^2)	Spot size (cm^2)	Number of sites	Distance from the tissue	Frequency	Duration
#1	632.8	31.25	40	1.0	0.8	18	<1 cm	Daily	From day after cessation of conditioning for 5 days
#2	650	1000 *	2	2.0	0.04	54-70	In contact	Daily	From 1st day of conditioning till day + 2 post-HSCT (for 7-13 days)

PBM (Laser/light) therapy

	LoE	Guideline category	Guideline
12	I	Recommendation	• The panel recommends the use of intra-oral PBM therapy using low level laser therapy for the prevention of OM in adult patients receiving **RT and CT for H&N cancer**. • Safety considerations unique to patients with oral cancer should be considered.

Protocol	Wave-length (nm)	Power density (irradiance; mW/cm^2)	Time per spot (sec)	Energy density (fluence; J/cm^2)	Spot size (cm^2)	Number of sites	Distance from the tissue	Frequency	Duration
#1	660	417 *	10	4.2	0.24	72	In contact	5 days / wk	Entire RT course
#2	660	625 *	10	6.2	0.04	69	In contact	3 days / wk (alternate days)	Entire RT course

Analgesics

Intervention: Morphine

	LoE	Guideline category	Guideline
21	III	Suggestion	Topical morphine 0.2% mouthwash is suggested for the treatment of OM-associated **pain** in **H&N** cancer patients treated with **RT-CT**.

Cryotherapy

	LoE	Guideline category	Guideline
22	II	Recommendation	The panel recommends using oral cryotherapy to prevent oral mucositis in patients undergoing **autologous HSCT** when the conditioning includes **high-dose melphalan.**

Cryotherapy

	LoE	Guideline category	Guideline
23	II	Recommendation	The panel recommends that patients receiving **bolus 5-FU chemotherapy** undergo 30 minutes of oral cryotherapy to prevent oral mucositis.

Natural remedies & Misc.

Intervention: Honey

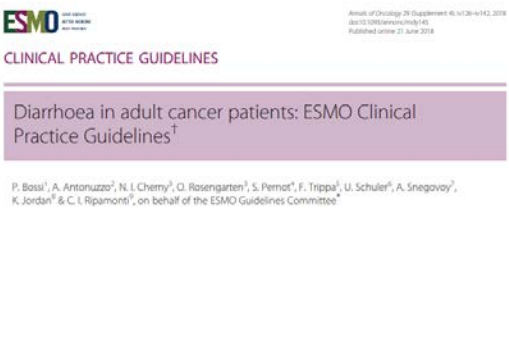
	LoE	Guideline category	Guideline
26	II	Suggestion	Honey is suggested for the prevention of OM in **H&N** cancer patients treated with either **RT or RT-CT**.

Growth Factors & Cytokines

Intervention: KGF-1

	LoE	Guideline category	Guideline
24	I	Recommendation	The use of KGF-1 intravenously is recommended for prevention of OM in patients with hematological cancer undergoing **autologous HSCT** with a conditioning regimen that includes **high dose chemotherapy and TBI**.

Immuno-related diarrhea: guidelines and new data



ESMO

CLINICAL PRACTICE GUIDELINES

Diarrhoea in adult cancer patients: ESMO Clinical Practice Guidelines†

P. Bossi[1], A. Antonuzzo[2], N. I. Cherny[3], O. Rosengarten[3], S. Pernot[4], F. Trippa[5], U. Schuler[6], A. Snegovoy[7], K. Jordan[8] & C. I. Ripamonti[9], on behalf of the ESMO Guidelines Committee*

CLINICAL PRACTICE GUIDELINES

Management of toxicities from immunotherapy

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

J. Haanen, F. Carbonnel, C. Robert, K. Kerr, S. Peters, J. Larkin and K. Jordan, on behalf of the ESMO Guidelines Committee

ESMO

ICI-induced diarrhea

- PD1/PDL1 → all grade 5-22%, grade 3-4: 1-3%
  CTLA-4 inhibitors → all grade 23-41%, grade 3-4: 3-10%
  Combinations → all grade 16-45%, grade 3-4: 2-10%

- It is a relatively early event
- Lesions predominate in descending colon and are characterized by erythema, edema, erosion, ulceration, bleeding

ICI-induced diarrhea

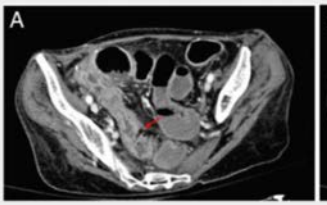


Figure 1 CT axial image during venous phase. Figure **A** shows a marked wall thickness (arrow) at the level of pre terminal ileum. Figure **B** shows a thicker wall of the ileum, with the presence of air (arrow), which is a typical sign of *pneumatosis* intestinalis, the lume is enlarged. These finding suggest the presence of necrosis of the ileum wall.

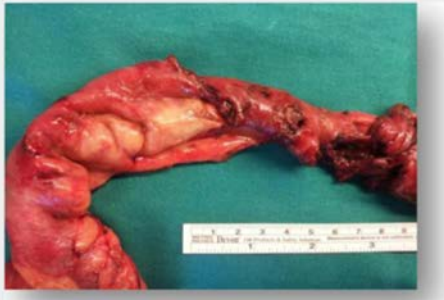


Figure 2 The picture show the last tract of ileum resected; as seen in this image the small bowel appearing necrotic and perforated in several points for at least 40 cm of length.

CLINICAL PRACTICE GUIDELINES

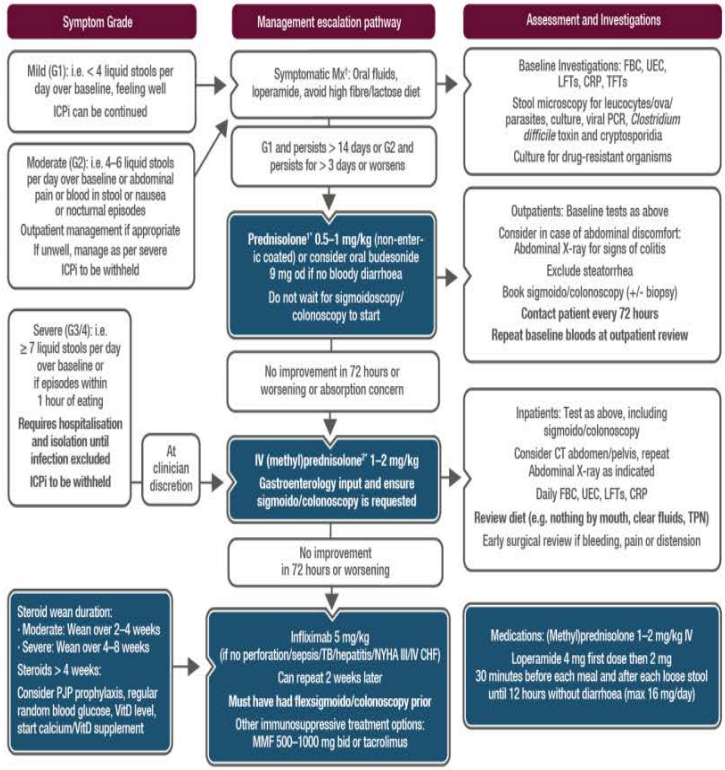
Immune related gastrointestinal toxicities

ICPi-related toxicity: Management of diarrhoea and colitis

[†]Loperamide 4 mg first dose then 2 mg 30 minutes before each meal and after each loose stool until 12 hours without diarrhoea (max 16 mg/day)

Steroid wean duration:
[1]Moderate: wean over 2–4 weeks
[2]Severe: wean over 4–8 weeks

[*]Steroids > 4 weeks: Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement



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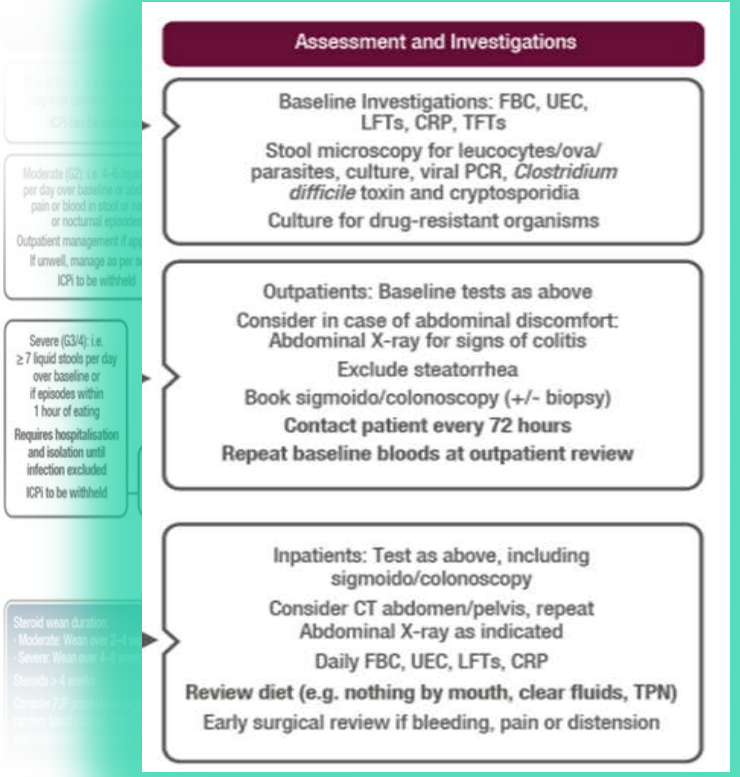
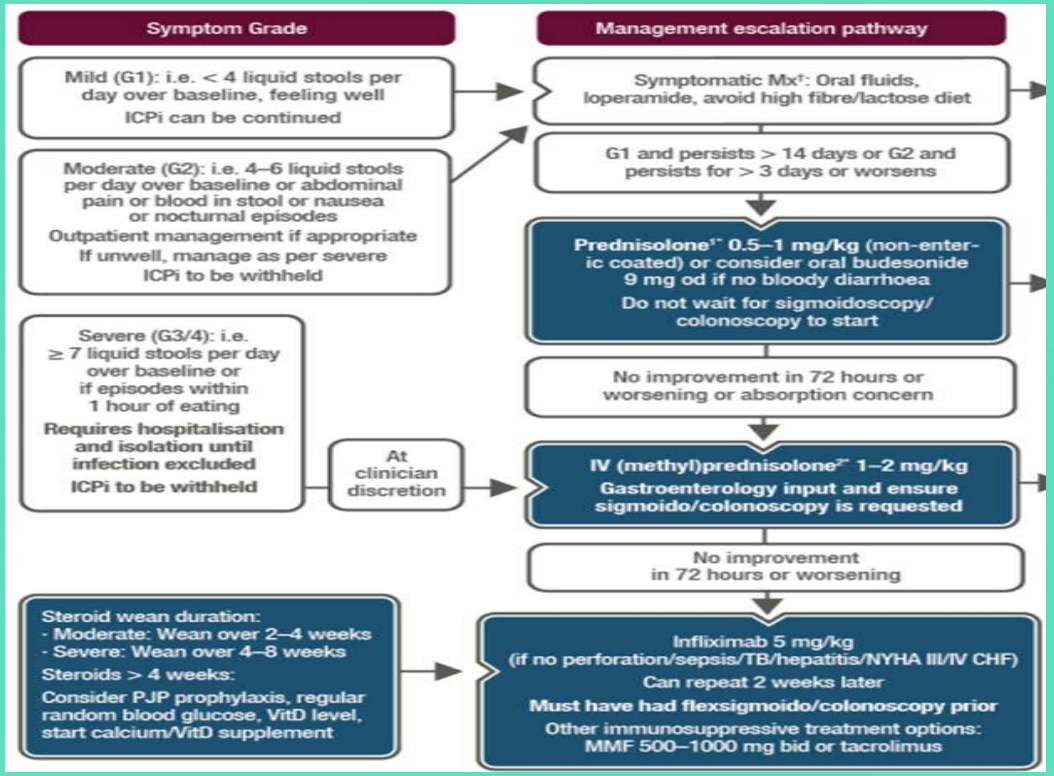

Assessment and Investigations
Baseline Investigations: FBC, UEC, LFTs, CRP, TFTs
Stool microscopy for leucocytes/ova/ parasites, culture, viral PCR, *Clostridium difficile* toxin and cryptosporidia
Culture for drug-resistant organisms
Outpatients: Baseline tests as above
Consider in case of abdominal discomfort: Abdominal X-ray for signs of colitis
Exclude steatorrhea
Book sigmoido/colonoscopy (+/- biopsy)
Contact patient every 72 hours
Repeat baseline bloods at outpatient review
Inpatients: Test as above, including sigmoido/colonoscopy
Consider CT abdomen/pelvis, repeat Abdominal X-ray as indicated
Daily FBC, UEC, LFTs, CRP
Review diet (e.g. nothing by mouth, clear fluids, TPN)
Early surgical review if bleeding, pain or distension
Severe (G3/4): i.e. ≥ 7 liquid stools per day over baseline or if episodes within 1 hour of eating
Requires hospitalisation and isolation until infection excluded
ICPi to be withheld


Symptom Grade
Management escalation pathway
Mild (G1): i.e. < 4 liquid stools per day over baseline, feeling well
ICPi can be continued
Moderate (G2): i.e. 4–6 liquid stools per day over baseline or abdominal pain or blood in stool or nausea or nocturnal episodes
Outpatient management if appropriate
If unwell, manage as per severe
ICPi to be withheld
Severe (G3/4): i.e. ≥ 7 liquid stools per day over baseline or if episodes within 1 hour of eating
Requires hospitalisation and isolation until infection excluded
ICPi to be withheld
At clinician discretion
Symptomatic Mx†: Oral fluids, loperamide, avoid high fibre/lactose diet
G1 and persists > 14 days or G2 and persists for > 3 days or worsens
Prednisolone†* 0.5–1 mg/kg (non-enteric coated) or consider oral budesonide 9 mg od if no bloody diarrhoea
Do not wait for sigmoidoscopy/colonoscopy to start
No improvement in 72 hours or worsening or absorption concern
IV (methyl)prednisolone²* 1–2 mg/kg
Gastroenterology input and ensure sigmoido/colonoscopy is requested
No improvement in 72 hours or worsening
Steroid wean duration:
- Moderate: Wean over 2–4 weeks
- Severe: Wean over 4–8 weeks
Steroids > 4 weeks:
Consider PJP prophylaxis, regular random blood glucose, VitD level, start calcium/VitD supplement
Infliximab 5 mg/kg
(if no perforation/sepsis/TB/hepatitis/NYHA III/IV CHF)
Can repeat 2 weeks later
Must have had flexsigmoido/colonoscopy prior
Other immunosuppressive treatment options:
MMF 500–1000 mg bid or tacrolimus

Open questions

Is it safe starting immunotherapy in pts with Inflammatory Bowel Disease (IBD)?

→ Patients with IBD experienced more high-grade diarrhea and colitis, more frequent requirements for add-on immunosuppressants, a higher risk of colonic perforation, and recurrent symptoms

→ Balance cost/benefit, provided that the autoimmune disease is well controlled without high doses of immunosuppresants

Kehl KL, et al. Cancer Immunol Immunother, 2019
Kennedy LC et al. J Natl Compr Canc Netw, 2019
Abu-Sbeih H, et al. J Clin Oncol, 2020

Open questions

Is it safe re-starting immunotherapy after an episode of immune-related diarrhea or colitis?

→ **Yes,** if grade 1 and controlled. **No** if grade 4.

→ Grade 2-3: if on CTLA-4 Inh, possible shift to PD-1/PD-L1 Inh
Consider: endoscopic features, PS, burden of disease, response to steroids, duration of irAE, immunotherapy benefit.

Abu-Sbeih H et al. J Clin Oncol, 2019
Brahmer JR et al. J Clin Oncol, 2018
Menzies AM et al. Ann Oncol, 2019

Open questions

Is it useful an earlier introduction of selective immunosuppressive therapy- SIT (infliximab, vedolizumab)?

→ No definitive response, trials ongoing.

→ Retrospective analysis showed a benefit of early introduction of SIT in less hospitalizations, better symptom management and steroid tapering

Clinicaltrials.gov: NCT04305145;
Abu-Sbeih H et al. J Immuno Cancer, 2019